

ORIGINAL PAPER

# Incidence of acute kidney injury in infants with dextro-transposition of the great arteries after arterial switch operation (an observational cohort single-center study)

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## ABSTRACT

**Introduction:** Transposition of the great arteries (TGA) is a type of congenital cardiac disease that affects 4.7/10,000 live births. The arterial switch operation (ASO) is the most preferred surgery to repair this anomaly. Cardiopulmonary bypass (CPB) is imperative to perform the operation. Prolonged exposure to the CPB can affect the liver, brain, kidneys, gastrointestinal tract, and heart. This study aimed to evaluate the effect of CPB on the development of acute kidney injury (AKI) in infants with TGA who underwent the ASO and to validate the applicability of neutrophil gelatinase-associated lipocalin (NGAL) for diagnosis of AKI.

**Material and methods:** The single-center study included 390 cases. All patients were classified using the pediatric risk, injury, failure, loss, end stage (pRIFLE) classification to assess the incidence of AKI. 360 cases were retrospective, and thirty cases were prospective; those thirty cases were assessed three times (before the operation, immediately postoperatively, and one week after the operation) with NGAL as a biomarker of renal tubular impairment.

**Results:** Among a total of 390 patients with transposition of the great vessels who underwent ASO, postoperative urea and creatinine showed a significant increase ( $p$ -value < 0.001), and a significant decrease was observed in postoperative glomerular filtration rate ( $p$ -value < 0.001). Around 40% of the patients showed positive postoperative AKI according to the pRIFLE classification. There was a significant increase in immediate and one-week postoperative NGAL levels in the thirty prospective cases. At the cut-off point serum NGAL concentration of 15.7 ng/ml, the sensitivity was 100%, and negative predictive value was 100%.

**Conclusions:** Acute kidney injury is a serious complication that can occur after open-heart surgery. Postoperative NGAL level could be a good indicator for postoperative AKI.

## KEY WORDS:

**acute kidney injury, cardiopulmonary bypass, arterial switch operation, neutrophil gelatinase-associated lipocalin.**

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## INTRODUCTION

Congenital heart diseases (CHDs) affect 0.8–1.2% of live births. Congenital heart diseases are classified according to the oxygen saturation into cyanotic and acyanotic heart disease. Dextro-transposition of the great arteries (D-TGA) is a type of congenital cardiac disease that affects 4.7/10,000 live births. The aorta emerges from the right ventricle while the pulmonary artery emerges from the left ventricle in this abnormality [1]. The arterial switch operation (ASO) is the preferred surgical approach for D-TGA in the absence of pulmonary stenosis. The pulmonary artery and aorta are translocated over their sinuses, and the ostia of the coronary arteries are re-implanted in the neo-aorta [2]. One of the most significant medical breakthroughs of the twentieth century was the creation of cardiopulmonary bypass (CPB) to allow heart surgery [3]. Cardiopulmonary bypass is the use of extracorporeal circulatory techniques in the repair of CHDs. It provides a pump to substitute the function of the heart and the lung, thus allowing the patient's heart and lungs to be temporarily devoid of circulation, so that cardio-thoracic surgery can be performed in a safe and controlled environment [4].

Acute kidney injury (AKI) is a sudden deterioration of normal kidney function that causes abnormal regulation of fluid, electrolytes, blood pressure, and removal of waste products [5].

Extended CPB can cause ischemia in the gastrointestinal tract, liver, kidneys, brain, and heart [6]. Acute kidney injury occurred in around half of the D-TGA neonates following ASO, and it was linked to lengthier hospitalizations in pediatric intensive care and hospitals [7].

Neutrophil gelatinase-associated lipocalin (NGAL) is a biomarker used to measure normal biological, pathological and pharmacological responses to therapeutic interventions [8]. Neutrophil gelatinase-associated lipocalin is considered to be a useful tool to diagnose and predict AKI outcome [9].

This study aimed to determine the impact of CPB on the development of AKI in infants with D-TGA after ASO and to validate the applicability of serum NGAL as a biomarker of renal injury in infants with D-TGA after ASO.

## MATERIAL AND METHODS

### STUDY DESIGN

An observational, cohort study.

### STUDY SETTING

Magdi Yacoub Global Heart Foundation provides cardiovascular care to adults and children in Egypt completely free of charge. The expenditure on the foundation is completely based on donations. It provide more than 2,000 pediatric cardiac procedures per year [10].

## STUDY POPULATION

A total of 390 cases were divided into two groups: 360 retrospective cases whose data were retrieved from patients' hospital records from 2015 to 2018; and 30 prospective cases whose data were collected during the study period (July 2019 – October 2019).

### INCLUSION CRITERIA

All infants suffering from D-TGA and undergoing ASO.

### EXCLUSION CRITERIA

A history of underlying renal diseases (diagnosed by impaired renal functions and pelviabdominal ultrasound), in preterm infants.

### DATA COLLECTION METHOD

D-TGA was diagnosed by echocardiography using a Philips EPIC7 machine. All patients with the inclusion criteria were subjected to the following: personal, perinatal, and family history, general and cardiac examination, and laboratory investigations including: complete blood picture, coagulation profile, serum electrolytes, liver and kidney functions.

Arterial switch operation details: the need for atrial septostomy or not, CPB time, aortic cross clamp (ACC) time, and blood products received.

The arterial switch operation was performed under general anesthesia, using low-flow hypothermic cardiopulmonary bypass. After cannulation and before starting cardiopulmonary bypass, the ductus arteriosus was ligated and divided and then a division of the aorta and pulmonary artery was done. After the transfer of coronary arteries, reconstruction of the pulmonary artery was done with autologous pericardium in all the patients. In patients with ventricular septal defect, a Gore-Tex patch was used to repair the ventricular septal defect.

All patients were classified by the pediatric risk, injury, failure, loss, end stage (pRIFLE) classification (using the estimated creatinine clearance method)\* to assess the AKI [5].

Pediatric risk, injury, failure, loss, end stage classifications:

- risk (R) – a 25% reduction in predicted creatinine clearance\*,
- injury (I) – a 50% reduction in predicted creatinine clearance\*,
- failure (F) – is defined as a 75% reduction in predicted creatinine clearance\*,
- loss (L) – renal function loss or impairment for more than four weeks,
- end-stage (E) – end-stage renal disease.

\* Using the Schwartz formula for calculation:  $\text{Length (cm)} \times K (\text{constant} = 0.5) / \text{serum creatinine}$

The thirty prospective cases were assessed 3 times (before the operation, immediately postoperatively, and one week after the operation) with serum NGAL as a biomarker of renal tubular destruction. Technique for sampling: Allow samples to clot for 2 hours at room temperature before centrifugation for 50 minutes, then collect the supernatant to carry out the assay.

The test principle: NGAL ELISA kit used the sandwich-ELISA principle. The micro ELISA plate provided in this kit has been pre-coated with an antibody specific to human NGAL. Standards for samples were added to the micro ELISA plate wells and combined with the specific antibody. Then a biotinylated detection antibody specific for human NGAL and avidin-horseradish peroxidase (HRP) conjugate were added successively to each microplate well and incubated. Free components were washed away. The substrate solution was added to each well. Only those wells that contain human NGAL, biotinylated detection antibody, and avidin-HRP conjugate appeared blue. The enzyme-substrate reaction was terminated by the addition of a stop solution and the color turned yellow. The optical density was measured spectrophotometrically at a wavelength of  $450 \pm 2$  nm. The optical density value was proportional to the concentration of human NGAL. Calculation of the concentration of human NGAL in the samples was done by comparing the optical density of the samples to the standard curve.

#### STATISTICAL ANALYSIS

Microsoft Office Excel Software Program 2019 was used to input pre-coded data into the computer. After that, the pre-coded data were uploaded and entered into the SPSS Statistics program, version 26, where it was statistically evaluated. All of the information gathered was double-checked for accuracy and logical consistency. The difference between matched groups for numeric parametric variables was analyzed using the paired *t*-test, Wilcoxon signed-rank test, and one-way repeated measured analysis of variance (ANOVA) test, with a *p*-value of less than 0.05 considered significant. A receiver operating characteristic (ROC) curve was performed to validate the postoperative NGAL as an AKI indicator.

#### STATEMENTS AND DECLARATIONS

The study was performed following the Declaration of Helsinki. Informed consent from a parent and/or legal guardian for study participation was obtained. The study has been approved by the Ethical Committee of the Department of Pediatrics, Faculty of Medicine, Ain Shams University, Egypt. The ethical approval number was FMASU MD 215/2019. Further information and documentation to support this are available to the Editor on request.

**TABLE 1.** Demographic and surgical data of the infants with transposition of the great vessels who underwent arterial switch operation

Parameters	Value (N = 390)
Age, days, median (range)	26 (1–120)
Sex, n (%)	
Male	270 (69.2)
Female	120 (30.8)
Consanguinity, n (%)	
Yes	66 (16.9)
No	324 (83.1)
CPB time (min) median (range)	161 (63–350)
ACC time (min) median (range)	95 (28–250)
Length of hospital stay (days) median (range)	15 (3–97)

ACC – aortic cross clamp, CPB – cardiopulmonary bypass

#### RESULTS

This study included 390 TGA patients who underwent ASO, and they were divided into two groups: 360 retrospective cases, and 30 prospective cases: 270 males representing 69.2%, and 120 females representing 30.8%. Individuals' ages varied from 1 to 120 days, with the median age at admission of 26 days. About 83.1% of patients were from non-consanguineous marriages. Atrial septostomy was necessary in 30.8% (120/390) of the patients. The cardiopulmonary bypass median time was 161 minutes, range 63–350 minutes, while the ACC median time was 95 minutes, range 28–250 minutes (Table 1).

As illustrated in Table 2, there was a significant increase in postoperative urea and creatinine (*p*-value < 0.001).

**TABLE 2.** Mean preoperative and postoperative laboratory tests of infants with transposition of the great vessels after arterial switch operation

Laboratory indicator	Value	<i>p</i> -value
Preoperative urea (mean ±SD)	21.1 ±13.7	< 0.001*
Postoperative urea (mean ±SD)	23.7 ±18.2	
Preoperative creatinine (mean ±SD)	0.3 ±0.1	< 0.001*
Postoperative creatinine (mean ±SD)	0.5 ±0.2	
Preoperative GFR (mean ±SD)	104.5 ±37.1	< 0.001*
Postoperative GFR (mean ±SD)	67.2 ±32.1	
Preoperative NGAL	15.8 ±2	< 0.001*
Postoperative NGAL	17.7 ±2.2	
One-week postoperative NGAL	18.5 ±2.1	

GFR – glomerular filtration rate, NGAL – neutrophil gelatinase-associated lipocalin, SD – standard deviation

\* Significant

<sup>a</sup> Please note that NGAL results were for the thirty prospective cases only.

Normal range is 5–18 mg/dl for urea, 0.3–1 mg/dl for creatinine, > 50 for the GFR, and 0.16–10 ng/ml for NGAL (reference: Edgar V Lerma EBS. Reference Range, Interpretation, Collection and Panels. 2019. <https://emedicine.medscape.com/article/2073979-overview>. Accessed 12 Nov 2022).

**TABLE 3.** Distribution of postoperative acute kidney injury among studied infants with transposition of the great vessels after arterial switch operation

Parameters	Value, n (%)
AKI (N = 390)	
Negative	235 (60.3)
Positive	155 (39.7)
RIFLE grade (N = 155)	
Risk	21 (13.6)
Injury	23 (14.8)
Failure	111 (71.6)
Use of furosemide (N = 390)	
Infusion	380 (97.4)
Shots	4 (1.0)
Not used	6 (1.5)
Use of PD (N = 390)	
Yes	134 (34.4)
No	256 (65.6)
Use of PD in positive AKI (N = 155)	
Yes	134 (86.4)
No	21 (13.6)

AKI – acute kidney injury, PD – peritoneal dialysis

In contrast, there was a significant decrease in postoperative glomerular filtration rate ( $p$ -value < 0.001).

According to the pRIFLE classification, postoperative AKI was found in 40% of our patients. The classification was as follows: Risk (21 patients); Injury (23 patients); and Failure (111 patients), as illustrated in Table 3. There was no statistically significant difference between the patients' age, sex, and AKI development ( $p$ -value 0.58, 0.945 respectively).

As shown in Table 4, CPB time and ACC time were increased significantly in positive AKI ( $p$ -value 0.012 and 0.009 respectively).

ANOVA was conducted to evaluate the change in patients' serum NGAL level when measured preoperatively, immediately postoperatively, and after 1 week postoperatively ( $n = 30$ ). There was a significant increase in serum NGAL level post-operatively and one week after the operation compared with the pre-operative level, as illustrated in Table 1.

Figure 1 demonstrates the validity measurement of immediate postoperative serum NGAL as a detector

of AKI. The area under the curve (AUC) was 75%, sensitivity was 100%, and negative predictive value (NPV) was 100% at the 15.7 ng/ml cut-off point.

## DISCUSSION

This study was conducted on 390 infants with D-TGA who underwent ASO at Magdi Yacoub Foundation, Aswan, Egypt.

Acute kidney injury associated with cardiac surgery is a major postoperative complication that can lead to a considerable elevation in perioperative morbidity and mortality [11].

In this study, postoperative AKI according to the pRIFLE classification was found in 40% of our patients. The classification was as follows: Risk (21 cases, 13.6%); Injury (23 cases, 14.8%); and Failure (111 cases, 71.6%). This was in line with a study performed on 85 children for postoperative AKI; they found that 38 (44.7%) had AKI. They were classified according to pRIFLE as follows: Risk (22 cases, 25.9 %); Injury (7 cases, 8.2 %); and Failure (9 cases, 10.6%) [12].

Another study was done on 1,489 pediatric patients who had heart surgery between January 2004 and December 2008. Acute kidney injury was found in 285 (20%) of the individuals according to the AKI network, 481 (34%) patients according to pRIFLE, and 409 (29%) patients according to the KDIGO system. The most sensitive test for diagnosing AKI was the pRIFLE system, particularly in the newborn age group (first year of life) [13]. A single-center, retrospective analysis of 71 cases of ASO in neonates with D-TGA showed that AKI developed in 50.7% [11].

In the current study, it was found that of all patients who developed AKI, 134 patients (34.6%) used peritoneal dialysis (PD). Harky *et al.*, in 2019, stated that AKI is a serious condition that necessitates the use of renal replacement therapy (RRT). PD was used to provide renal replacement treatment to 11.1% of patients [11].

In 2018, Al-Ayed *et al.* evaluated the impact of PD on fluid balance and consequence syndrome in the maintenance of newborns who had undergone heart surgery. They found that 27 (33%) of 81 consecutive infants who received cardiac surgery needed PD [14].

In this study, we measured the NGAL in 30 patients who underwent ASO. About 21 patients from the 30 prospective cases experienced positive AKI. There was a significant elevation in serum NGAL level postoperatively

**TABLE 4.** Relation between patient cardiopulmonary bypass and aortic cross clamp time and acute kidney injury development in infants with transposition of the great vessels after arterial switch operation

Parameters	Negative AKI	Positive AKI	$p$ -value
CPB time (min)	158.8 ±54.7	174.2 ±61.5	0.012
ACC time (min)	94.6 ±35.5	105.8 ±42.7	0.009

ACC – aortic cross clamp, AKI – acute kidney injury, CPB – cardiopulmonary bypass

and one week after the operation related to the preoperative level. There was a significant elevation in immediate postoperative serum NGAL in positive AKI patients ( $p$ -value = 0.04).

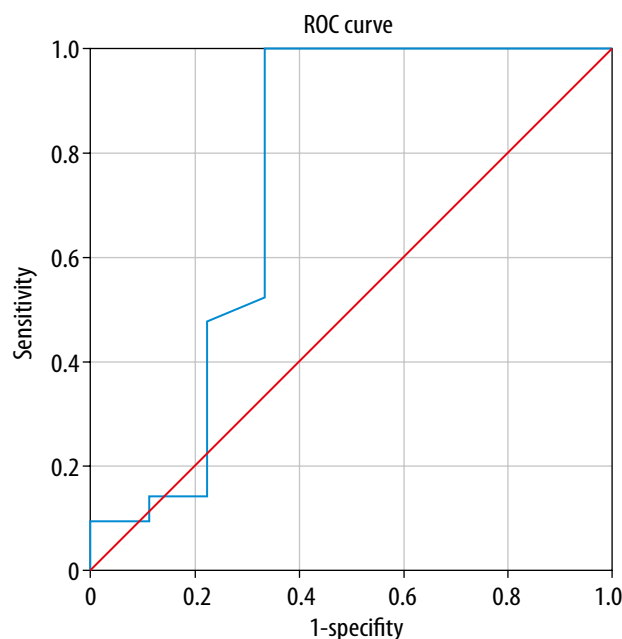
A meta-analysis of data from 19 studies comprising 2,538 individuals from eight countries and 487 cases (19.2%) of AKI was performed. Neutrophil gelatinase-associated lipocalin concentrations in plasma, serum, or urine are diagnostic and predictive for AKI, RRT, and death, according to the researchers, particularly in children who have had cardiac surgery [15].

We recommend the measurement of immediate postoperative serum NGAL as a detector of AKI, where the AUC is 75%, sensitivity is 100%, and NPV is 100% at the cut-off point of 15.7 ng/ml.

The clinical importance of the new biomarker NGAL for the early detection of AKI was studied by Zhang *et al.* [16]. They examined 38 severely ill individuals with AKI and 38 severely ill individuals without AKI in the observation and control groups. At 2, 8, 12, and 24 hours after surgery, serum NGAL, serum creatinine (SCr), and cysteine protease inhibitor cystatin C (CysC) were measured in serum. At several time points after surgery, no significant differences in SCr levels were identified between the two groups, while NGAL and CysC levels in the observation group were considerably greater than in the control group. The levels of NGAL and CysC were favorably associated with Scr levels, according to a Pearson correlation coefficient analysis. The area under the AKI curve for NGAL in early diagnosis was 90.4%, the sensitivity was 90.2%, and the specificity was 89.5%. In earlier detection, the area under the AKI curve for CysC was 80.6%, the sensitivity was 79.2%, and the specificity was 78.5%. The area under the AKI curve for SCr in early diagnosis was 63.4%, the sensitivity was 64.2%, and the specificity was 62.5%. As a result, they concluded that NGAL has good early predictive value for AKI and can be employed as a biomarker for AKI diagnosis [16].

In 2016, a meta-analysis was conducted to explore the diagnostic accuracy of NGAL in the early postoperative diagnosis of cardiac surgery associated with AKI (less than 12 hours). Neutrophil gelatinase-associated lipocalin was found to be one of the early AKI biomarkers since its rise occurred before the rise in SCr, which could occur many days later. Urine NGAL could be a cost-effective and faster way to diagnose AKI [17].

In 2016, Afify *et al.* suggested that serum NGAL could be used as an early biomarker for AKI, as it increased considerably with the severity of renal dysfunction. The serum NGAL cut-off value of 40 ng/ml within the first 24 hours after admission, according to ROC analysis, is extremely specific and sensitive for indicating AKI, with a sensitivity of 90.9% and a specificity of 75.8%. They concluded that measuring serum NGAL levels early in sepsis can be a therapeutically relevant sign for predicting AKI and assessing its severity [18].



**FIGURE 1.** Validity measurement of immediate postoperative serum neutrophil gelatinase-associated lipocalin  
*Diagonal segments are produced by ties.*

## CONCLUSIONS

Acute kidney injury is a serious complication that can occur after open-heart surgery. Postoperative NGAL level could be a good indicator for postoperative AKI.

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## DISCLOSURE

The authors declare no conflict of interest.

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